REVIEW ARTICLE

Cystic Fibrosis

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■ *Cystic fibrosis, a disease thought to be transmitted as a recessive genetic trait, is found as a disease in about one in 1,000 to one in 10,000 births. It involves all of the exocrine glands with presenting symptoms dependent upon the extent of involvement of any group of glands. Many aspects of the disease can be corrected by substitution therapy. This applies particularly to the use of animal pancreas for the steatorrhea and salt for prevention of heat prostration. Unfortunately, the obstructive pulmonary disease with secondary bronchial infections can only be treated symptomatically by the use of mucus thinning agents, postural drainage, and antibiotics. Nevertheless, longevity can be increased and a great deal of hope offered to the families of these unfortunate children by careful supervision of their medical care.*

CYSTIC FIBROSIS has been recognized as a distinct clinical entity since the late 1930's.[2,16] In the intervening years, it has been called a variety of names thought to be more descriptive, including *fibrocystic disease, mucoviscidosis* and, most recently, *diffuse exocrinopathy*. The original and still generally recognized name of cystic fibrosis was based upon the observation that certain children with steatorrhea who died from chronic lung infections had fibrosis and cystic changes in the pancreas at autopsy. Subsequently, it was shown that the mucus secretions of the body were much more viscid than usual, thus the term *mucoviscidosis*.[10] The most recent proposal that the disease be called diffuse exocrinopathy[6] comes from the demonstration that all of the exocrine glands of the body may produce secretions that are in some manner abnormal. This, too, is still only descriptive and not likely to replace the original name of cystic fibrosis.

Etiology

Cystic fibrosis is recognized as a disease of genetic origin, believed to be transmitted as a Mendelian recessive.[22] As such, the recessive gene must be conferred to the child by both parents in order for him to have the disease. There is no family history of the disease except in siblings and cousins. Reports from various clinics have indicated an incidence in siblings of one out of four. Our own verified data on 100 families indicates that 150 out of a total of 329 children were affected, an incidence of 45 per cent.

No method has yet been devised to identify the heterozygote or gene carrier. Although parents of children were at one time thought to have unusually high sweat electrolytes, subsequent studies[1,15] have shown this not to be higher than in the general population of adults. Nor has it been possible to confirm a higher incidence of pulmonary or gastrointestinal problems in ancestors of children with

Further information, lay or medical, can be obtained by writing the National Cystic Fibrosis Research Foundation, 521 Fifth Avenue, New York 17, New York. Information regarding location of Cystic Fibrosis Centers are also available through this source.

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cystic fibrosis. Studies on families of children from this clinic failed to demonstrate an incidence of such diseases greater than that seen in controls.[12]

The gene is believed to be a very common one, estimated to occur in about one out of thirty persons in the general population. This results in an observed disease frequency of about one out of every 3,600 births, although it has been variously reported as occurring in from 1:1,000 to 1:10,000.[11,19]

It is very uncommon in some racial groups such as Negroes and Orientals. Out of a total of 321 patients seen at Childrens Hospital, only three were Negroes and none were Orientals. The disease is relatively uncommon in Latin Americans. In spite of the fact that Los Angeles has the largest Latin American population of any city north of Mexico City, there were only seven patients of Latin American origin in our series.

Symptoms and Signs

In most cases the disease is diagnosed during the first few years of life. In 130 of the 321 patients in the present study diagnosis was made when the patient was less than one year of age, and in most of the remainder by five years of age. However, three of the patients were 11 years old at the time of diagnosis, one was 14 and one was 17 (Table 1).

Although greater awareness of the disease among physicians will undoubtedly result in earlier diagnosis, severity of symptoms will continue to vary greatly from patient to patient. The child with large, bulky, greasy, foul smelling stools who fails to thrive in spite of a voracious appetite and who has chronic or recurrent pulmonary infections, presents little difficulty in identification. Such a patient is seen in Figure 1. He is thin, has a prominent abdomen and wasted buttocks. Muscle tone is poor. Intercostal retractions may be seen on inspiration and the expiratory phase may be prolonged.

Not all patients so obviously have the disease, for symptoms will depend upon the extent of involvement of the various exocrine glands of the body including sweat glands, lacrimal glands, salivary glands, pancreas, liver and mucus-secreting glands of the tracheobronchial tree and gastrointestinal tract.

TABLE 1.—*Age of Children Followed at Cystic Fibrosis Center When Diagnosis Was Established.*

Under 1 yr.	130
I year	50
2 years	33
3 years	25
4 years	18
5 years-9 years	39
Over 10 yrs.	6

Sweat of most patients contains a high concentration of electrolytes. The sweat tastes salty and they cannot conserve salt under conditions of heat stress. Excessive sweating results in salt crusting, especially at the hair line of the forehead. During hot weather, heat prostration may develop with very low serum sodium and chloride values unless these electrolytes are replaced. Ten of our patients had heat prostration.

Tears and saliva also contain higher than usual concentrations of salt.[7] Although it is not lost in sufficient quantities to cause symptoms, salivary gland enlargement as shown in Figure 2 has been

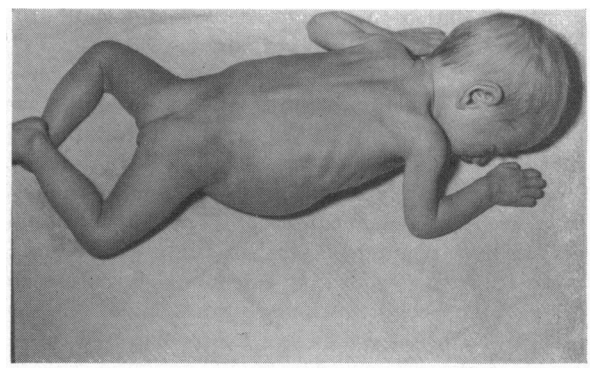

Figure 1.—Infant with loss of subcutaneous fat, protuberant abdomen, poor muscle tone and intercostal retractions.

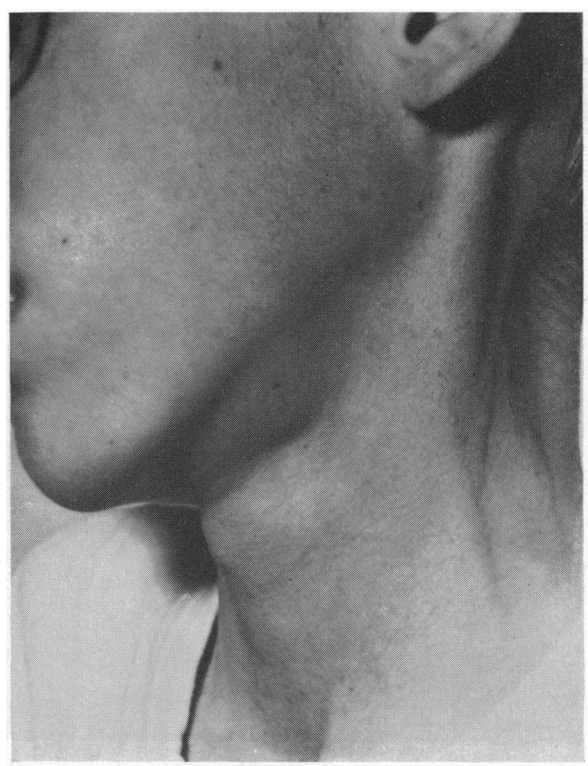

Figure 2.—Submaxillary gland enlargement made more evident by loss of subcutaneous fat.

observed[3] and was noted in 30 patients in the present study.

Reports indicate that the pancreas produces inadequate amounts of enzymes for digestion of food in about 85 per cent of patients.[20] Approximately the same proportion (91 per cent) of patients in this series had steatorrhea. The amount of pancreatic insufficiency is quite variable, ranging from the condition in which the stools are a little loose and foul smelling at times in a child with an average appetite and normal growth, to that in which a child with severe pancreatic insufficiency is thin and wasted in spite of a voracious appetite.

The earliest manifestation of pancreatic insufficiency is that of meconium ileus in the newborn. This was the presenting symptom in 38 cases (11 per cent) in the present series. These infants have intestinal obstruction at birth, with a distended abdomen and vomiting. If the ileum has ruptured in utero, meconium peritonitis will be present and may show up on a plain film of the abdomen as multiple areas of calcification. (Figure 3.) Intestinal atresia may result from such a rupture; therefore cystic fibrosis should be considered in all such babies.[9] The colon is small from lack of function and can be demonstrated as a microcolon by barium enema studies (Figure 4).

Other complications of the pancreatic insufficiency with resulting abnormal stools are rectal prolapse, which occurred in 56 patients (17 per cent), nutritional edema and intestinal obstruction in older children. The latter, while uncommon, has been the subject of a report from this hospital.[21]

The biliary tree is involved in some cases of cystic fibrosis. Jaundice may develop during the early months of life, probably due to inspissated bile. One infant, for example, had a bile cast of the gallbladder at the time of death. Nine children had cirrhosis and eight of the nine also showed evidence of portal hypertension. It is probable that this will be observed more often as children live for longer periods.

By far the most serious problem is that of recurrent respiratory tract infection. Although this factor is not well documented in this series, it is believed that most children with cystic fibrosis have sinusitis. Nasal polyps are not uncommon and are associated with a chronic mucoid or mucopurulent nasal discharge, often mistakenly thought to be due to allergic disease.

The most serious aspect of the disease is involvement of the lower respiratory tract. The normal child has a thin, watery blanket of mucus covering the entire tracheobronchial tree. It is constantly being renewed and swept up to the pharynx by the action of the cilia. It carries with it inhaled foreign material such as dust or bacteria. Children with cystic fibrosis appear to have a thicker, more sticky mucus which does not move as readily, thus allow-

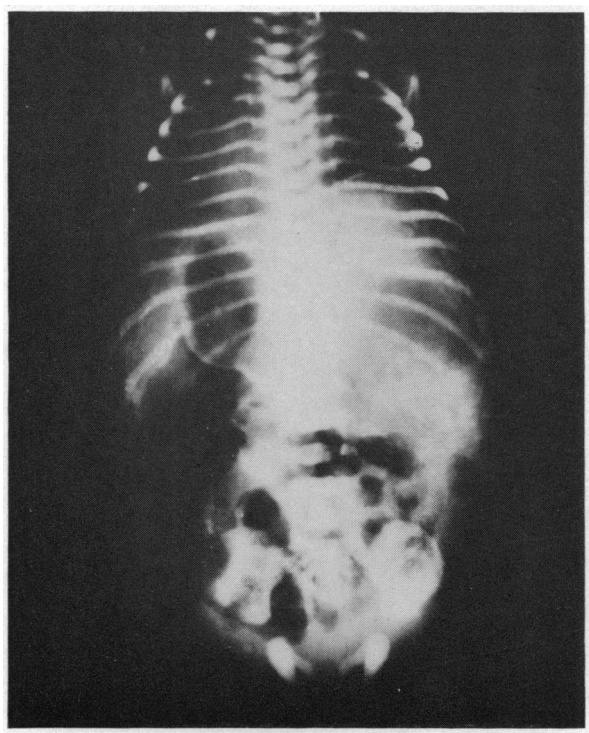

Figure 3.—Meconium ileus with rupture of the small bowel in utero followed by ileal atresia. Note calcification due to meconium peritonitis.

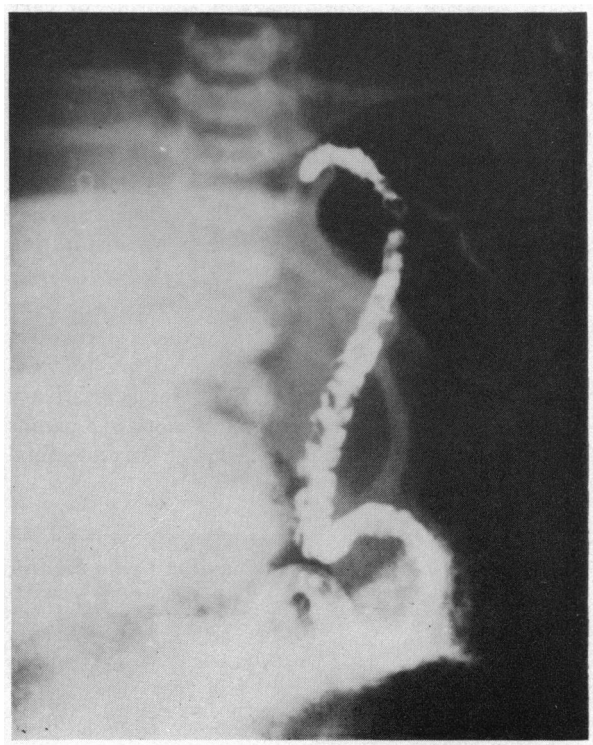

Figure 4.—Microcolon demonstrated by barium enema.

ing bacterial growth. Plugging of the bronchi and bronchioles results from these secretions, and the normal respiratory bacterial flora then grow more readily. Bacterial toxins produce inflammation with mucosal swelling and exudate, which in turn produces more airway obstruction. Bronchi expand on inspiration and contract on expiration, allowing air to enter more easily than it can be expired, with air trapping resulting. In time, the anterior-posterior diameter of the chest increases (Figure 5). X-ray films of the chest reveal increased radiolucency of the lungs, increased anterior-posterior diameter of the chest and bowing of the sternum (Figure 6).

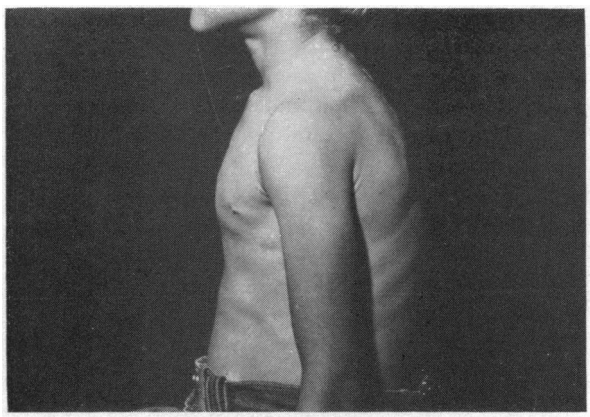

Figure 5.—Lateral view of child with extensive air trapping manifest by increased AP diameter of the chest.

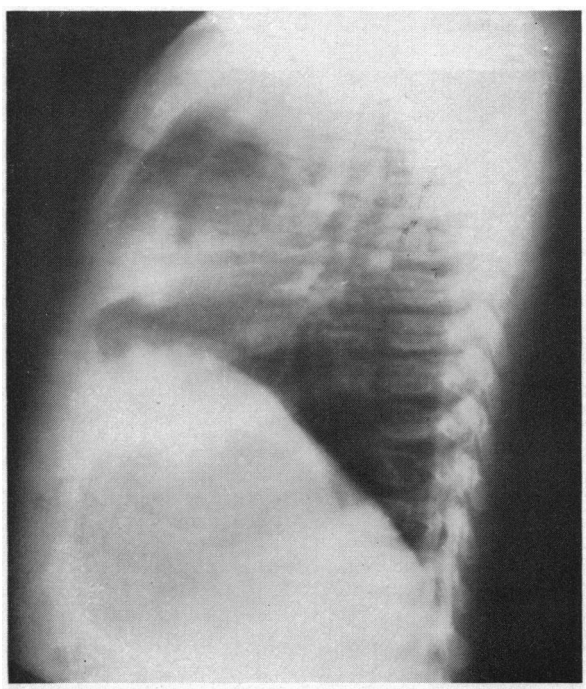

Figure 6.—X-ray of child with cystic fibrosis that demonstrates earliest x-ray changes—increased radiolucency of lungs with bowing of sternum, increased AP diameter of chest, and right middle lobe pneumonia.

Pneumonia develops easily. With complete obstruction of the bronchi segmental atelectasis and chronic pneumonitis develop and in x-ray films streaking up to the upper lobes may be seen. Bronchiectasis and lung abscesses follow. The cough, which at first may be dry and irritating, becomes productive, paroxysmal and exhausting. Dyspnea with intercostal and suprasternal retractions becomes more pronounced. The accessory muscles of respiration are used and the chest becomes almost fixed in the position of inspiration, with breathing primarily diaphragmatic.

The child improves as infection is brought under control. However, virus infections of a kind that often involve the lower respiratory tract (such as influenza, measles and many unidentified viruses) tend to reactivate the process again and again until the child finally dies of pulmonary insufficiency.

Cor pulmonale, manifested by edema, enlarged liver, enlarged heart with right ventricular hypertrophy and dilated neck veins, may be present in the late stages of the disease but appears to be largely associated with hypoxia. It is usually reversible if the pulmonary infection can be controlled.

Clubbing of the fingers and toes generally appears early and parallels the severity of the lung disease. It is so rare in other types of chronic lung disease in children that cystic fibrosis must be suspected when clubbing is observed.

Diagnostic Aids

If attention is drawn to a child because of chronic diarrhea, foul, greasy, bulky stools, recurrent or chronic lower respiratory tract infection, wheezing, unexplained heat prostration or meconium ileus in a newborn, certain laboratory studies are helpful in establishing the diagnosis. By far the most useful laboratory aid is a determination of the sodium or chloride content of the sweat. This procedure is rapid and causes minimal discomfort. Sweat is collected from an area of skin that has been made to sweat profusely by pilocarpine iontophoresis. It is then analyzed for salt content. Reports indicate that 98 per cent of children with cystic fibrosis have sweat chlorides in excess of 50 mEq per liter. In normal children the sweat chloride rarely reaches 50 mEq per liter. Moreover, elevated sweat chlorides are found in only a few other clinical conditions, including adrenal insufficiency, hypothyroidism and some types of ectodermal dysplasia. In our experience, only one child with cystic fibrosis had sweat chlorides below 50 mEq per liter. In two the content was between 50 and 70 mEq per liter, and 29 per cent of the patients had sweat chloride content between 70 and 100 mEq. In the remainder it was more than 100 mEq. This correlates with reports from other centers.[1,15] The test is of limited

value after the child reaches the age of puberty, for at that time many normal persons will have sweat chloride content in excess of 50 mEq per liter. It should be pointed out that sweat chloride determinations in the average clinical laboratory are subject to many errors, both in the collection of the sweat and in the determination of the electrolyte content. The diagnosis should not be made on the basis of this single laboratory procedure.

Pancreatic insufficiency resulting in some degree of steatorrhea is present in 85 to 90 per cent of children with cystic fibrosis. A standard diagnostic procedure before the development of the sweat test was duodenal intubation and collection of pancreatic fluid which could then be analyzed for enzyme content. This procedure is now done infrequently because it is difficult and very unpleasant for the patient. It is subject to many errors and is now used only in the most unusual diagnostic problems. Lipiodal and Vitamin A absorption studies are of limited value, for they can demonstrate only that poor absorption took place at the time of the examination. A much more reliable procedure for the confirmation of steatorrhea is the measurement of fat excreted in the feces over a period of from 24 to 72 hours.[8] The presence of excessive amounts of fat of course does not differentiate cystic fibrosis from the malabsorption syndromes, and this determination is therefore of limited value for diagnosis.

The second most useful diagnostic aid is x-ray study of the chest. Air trapping is a significant early feature of the disease and it may be noted in film showing no other abnormality. When air trapping is accompanied by a patchy peribronchial infiltrate which extends particularly into the upper lobes, it is almost pathognomonic of cystic fibrosis (Figure 7). Areas of chronic pneumonia and segmental atelectasis are common. Spontaneous development of pneumothorax must always arouse suspicion of cystic fibrosis.

Other useful x-ray studies are those of the sinuses, and evidence of sinusitis is frequently seen. X-ray studies of the gastrointestinal tract, using contrast medium, reveal puddling of the media in the small bowel (Figure 8) and a "cobblestone" appearance of the colon due to pseudopolypoid changes (Figure 9). An extensive review of x-ray findings has been published.[23]

Treatment

Therapy will depend upon the patient's symptoms, which will be related to the extent of the involvement of the various exocrine glands.

Sweat Glands. Almost all patients lose abnormal amounts of salt in their sweat and an increase in dietary salt is necessary to replace it. This can usually be accomplished by allowing a child who is old enough free use of the salt shaker. However, under conditions of heat stress, salt tablets may be necessary. If persistent vomiting should occur during a heat wave, preventing oral replacement of salt, severe hypoelectrolytemia may develop within a matter of hours. The family must be warned of this and the child brought in for intravenous infusion of salt solutions without delay.

Pancreas. Eighty-five to 90 per cent of patients with cystic fibrosis have some degree of pancreatic insufficiency. This ranges from mild steatorrhea requiring only a reduction of dietary fats, to complete absence of pancreatic enzymes, resulting in large, foul, frothy, extremely maladorous stools with oil droplets on the water. Children with fairly adequate pancreatic enzymes may have normal growth and development with good muscle tone while the latter group will be thin and wasted, have pot belly, little subcutaneous fat and poor muscle tone.

Administration of pancreatic enzymes* to the latter group usually results in decided improvement in growth and development. Muscle tone improves, subcutaneous fat is added and, in time, even the pot belly is lost. There seems to be little general advantage of one type of preparation over another. The patient's or the physician's preference appears to be an individual matter. Powder or granules sprinkled on the food or taken just before a meal

*Panteric® tablets or granules (Parke Davis Co.), Viokase® powder or tablets (Viobin Corporation), Cotazyme® capsules or powder (Organon, Inc.), Entozyme® tablets (A. H. Robins Laboratories), and Pankrotanon® granules or powder (Hausmann Laboratories, St. Gallen, Switzerland).

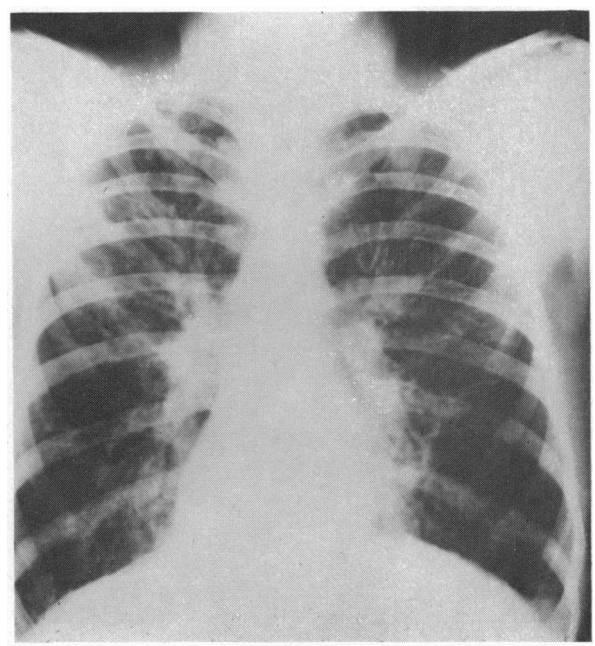

Figure 7.—X-ray of the chest showing advanced changes consisting of air trapping and perihilar infiltrates extending particularly into the upper lobes.

are necessary for infants and small children while capsules or tablets are preferred by older children. Sometimes it is necessary to try several brands before the best product is found for a particular child. Probably the most common error of treatment is failure to recommend an adequate amount. It is best to start with one-fourth teaspoonful of powder or granules per feeding for small children or one tablet or capsule per meal for older children. The dosage should be increased slowly over a period of several weeks until there is no further decrease in the frequency, volume or greasiness of stools. If the stools are still abnormal after one teaspoonful of powder or four capsules or eight tablets per feeding, then the dietary fat should be restricted by using either skim milk or 2 per cent butterfat milk, cutting the fat off meat and avoiding other fried and greasy foods.

Infants with meconium ileus require special care. After operation to remove the intestinal obstruction, a prolonged period of parenteral alimentation is often necessary. Attempts should be made to give nearly adequate calories and vitamins from the first. When food can be taken by mouth, either Nutramigen® without pancreatic enzymes added or Probana® with additional enzymes seems to be best tolerated. Vitamin K should be given for several months to prevent bleeding from hypoprothrombinemia, especially to infants who have had resection of the small bowel.

Serum proteins are often quite low because of poor absorption. In addition to this, some patients may first come to medical attention because of generalized edema due to secretion of protein into the bowel. In the present series six patients who had hypoproteinemia associated with exudative enteropathy, when they were first examined, were found to have cystic fibrosis. They improved with administration of serum albumin, high protein diet and oral pancreatic enzymes.

Rectal prolapse as a result of the voluminous stools, poor muscle tone and loss of subcutaneous fat used to be common.[13] The condition was present in 56 patients in the series when they were first seen. It responded well to adequate diet and pancreatic enzymes, but occasionally taping of the buttocks for a few weeks was necessary. Fortunately, prolapse is seen infrequently nowadays, owing to prompt diagnosis and treatment.

Liver. Cirrhosis is not unusual, especially in older children. This may result in portal hypertension with splenomegaly, ascites, lower extremity edema, and bleeding from esophageal varices. Often considerable improvement can be effected by good diet, administration of pancreatic enzymes, control of infections in the lungs and the use of diuretics. Surgical shunting of the portal blood to the caval system may be considered for patients with sufficient respiratory reserve to tolerate the operation. Each case must be considered separately.

Tracheobronchial tree. Treatment must be tailored to the individual child. Bronchopulmonary

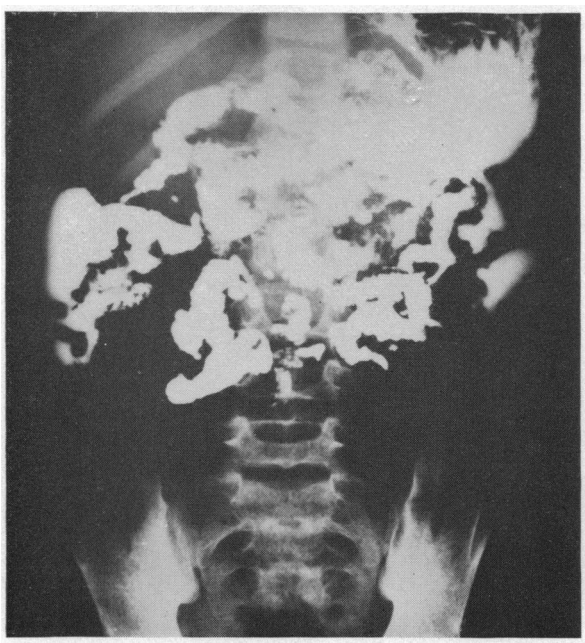

Figure 8.—Small bowel x-rays showing puddling of barium also noted in malabsorption syndromes.

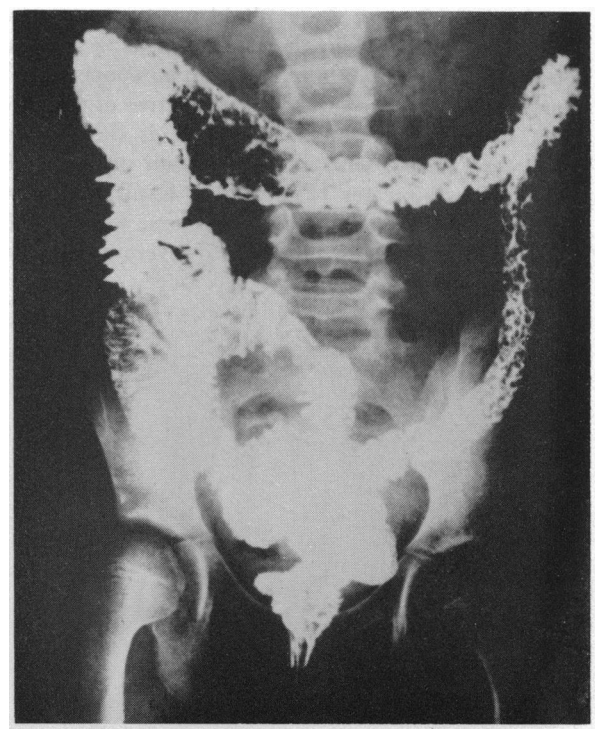

Figure 9.—Post evacuation x-ray of barium enema. Note "cobblestone" appearance of mucosa due to pseudopolypoid changes.

infections are the most serious problems encountered and are the cause of almost all deaths. The basic principles of management of purulent infections should be followed. These consist of drainage and administration of appropriate antibiotics. During the early stages of the disease, staphylococcus is usually cultured. Although species of hemophilus are cultured infrequently, it has been shown that most patients have high antibody titers indicating frequent infections. Exacerbation of pulmonary symptoms may also be caused by the usual pathogenic pneumococcus and B streptococcus. When antibiotics have been used extensively and severe lung disease has developed, pseudomonas and other gram-negative organisms tend to predominate.

Sputum cultures should be obtained as indicated by the patient's progress and used as a guide for rational antibiotic therapy. Decision between the use of continuous antibiotic therapy and therapy of acute infections will depend upon the patient's response. When maximum response has been obtained after several weeks of antibiotic therapy, the drugs may be discontinued and the patient observed frequently for evidence of deterioration. The most useful measurement of patient response is his weight. Improvement almost invariably results in weight gain; deterioration, in weight loss. Respirations and pulse rate are useful if obtained under resting conditions but are of little value in apprehensive children. Expansion of the chest measured in circumference at the xyphoid process on forced expiration and maximal inspiration is a helpful observation in patients old enough to cooperate. A very useful tool for following the course of patients with obstructive pulmonary disease is the Wright peak flow meter, with which one can obtain peak expiratory flow rates (Figure 10). Expiratory flow rates are influenced by many factors, which limit the value of absolute figures. However, the results obtained closely parallel the progress of the disease in an individual patient. Findings on auscultation of the chest and on chest x-ray examination are sometimes confusing, for both may appear to be worse when the patient is better and vice versa.

Antibiotics are generally administered by mouth. The most useful drugs are the tetracyclines, although they have the disadvantage of staining the teeth. Erythromycin and penicillin will control infection when the organisms are sensitive to them. In spite of its toxicity, chloramphenicol has proven to be a particularly valuable drug. The effects of oxycillin may be dramatic when dealing with resistant strains of staphylococcus. Drugs that cannot be administered orally but are extremely useful for treatment of pseudomonas are streptomycin, polymyxin and colymycin. Any antibiotics that can be given by injection may also be given by aerosol (Figure 11). With the exception of polymyxin and colymycin, which are used in a concentration of 4 mg per ml, they are given in a concentration of 50 to 100 mg per ml. One to two milliliters is administered by aerosol three to four times daily. As it has a broad spectrum of effectiveness, and may have serious toxic effects when given parenterally, neomycin is the antibiotic most commonly administered by aerosol.

A number of other agents including proteolytic

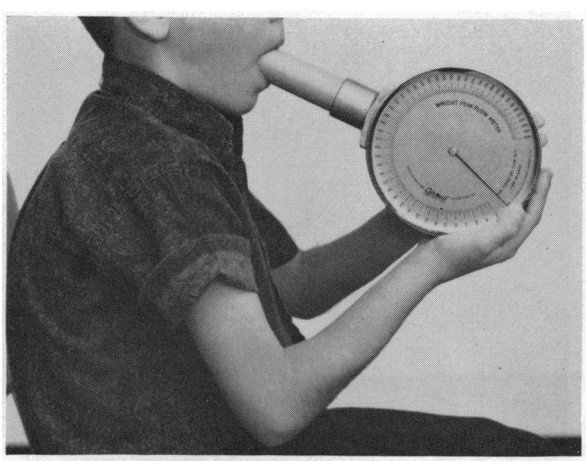

Figure 10.—The Wright peak flow meter for obtaining peak expiratory flow rates.

Figure 11.—Mask nebulizer powered by a motor driven compressor used for administering medication by aerosol.

enzymes, desoxyribonuclease, detergents and mucolytics have also been given by aerosol. They have not found wide acceptance, however, either because of toxicity or in adequate therapeutic response. The most recently introduced product of this type is N-acetylcysteine,* which has been shown to have a liquefying effect *in vitro* on thick, tenacious mucoid secretions. It has been extensively studied[5,17,18] and found to be relatively non-toxic with side effects consisting of rhinorrhea, vomiting and nausea. In an occasional patient it may cause bronchospasm. It appears to be useful for some patients who have not responded adequately to other therapeutic measures. It has been very difficult, however, to objectively demonstrate its value. For example, 15 patients with relatively stable disease received 3 ml of 20 per cent N-acetylcysteine three times daily by aerosol and 15 others received a placebo for two months. None became worse. One of those receiving the placebos said he was having less cough, as did five of those receiving the active agent. Two patients, who were receiving the N-acetylcysteine, gained weight and one had an improvement in peak expiratory flow rate. It is believed that failure to respond is due less to lack of activity of the drug than to inability to deposit the droplets in the affected bronchi and bronchioles.

Mist tents are now being utilized more extensively. Children sleep in them throughout the night and sometimes during the day, breathing nebulized distilled water or 10 per cent propylene glycol in distilled water to thin bronchial secretions and thus facilitate removal by ciliary action and coughing. Two studies have been done in an attempt to demonstrate their effectiveness. One by Matthews[14] in Cleveland showed an improvement in pulmonary function in the majority of patients after tent therapy was begun. The other, by Barbero[4] in Philadelphia, failed to show any overall improvement in a group of patients as compared with controls after one year of mist therapy while sleeping. My own impression has been that some patients do indeed show improvement and others do not benefit. Some, including most adolescents, will discontinue the mist after a trial of several weeks.

The most satisfactory equipment for home use, in our experience, has been the MistO_2Gen† Model #HT15-5 tent, nebulizer and compressor which produces a good quantity of mist of a particle size between 0.5 and 10 microns when 10 per cent propylene glycol in distilled water is used as the nebulized material. Other equipment may work equally well but our experience has been limited. Ultra-sound nebulizers produce a large quantity of fine mist but have not received adequate clinical trial and are expensive. Units used for aerosol therapy must produce a mist of a particle size ranging from 0.5 microns to no greater than 10 microns to assure precipitation of the droplets on the surface of the smaller bronchi and bronchioles. Most units, including croup tents utilized in hospitals, fail to do this. Their effectiveness can be increased, however, by adding a MistO_2Gen Varitrol nebulizer to the hospital croup tent. Compressed air supplied from a tank or a motor-driven compressor should be used unless the patient is cyanotic, in which case oxygen may be substituted. Many patients, especially those with some element of congestive heart failure, are more comfortable in oxygen. Some find they do well just using it at night.

Bronchodilators, expectorants and mucus-thinning agents may be given by mouth. These include ephedrine, aminophylline, saturated solution of potassium iodide and glyceryl guaiacolate. It is difficult to demonstrate the value of these agents but if an individual patient benefits, then they should be used. Potassium iodide has the disadvantage of producing goiter and acne in some patients.

Postural drainage with clapping and vibration over all segments of the lung may be very helpful. Physical therapists should be trained to carry out these procedures and to teach parents.

It is important that general pediatric care not be neglected, that the patients receive the usual immunizations, and, in particular, that measles and influenza vaccines be administered. General physical activity should be allowed and muscle building exercises encouraged. One patient who decided at 16 years of age that he was tired of being frail and weak, had become a top-notch weight lifter by age 21.

Prognosis

Life expectancy is limited by the severity of the respiratory disease although it may be increased many years by vigorous therapy. For example, before the establishment of the Cystic Fibrosis Center at Childrens Hospital of Los Angeles, 50 per cent of the children who had the disease were dead before the age of five years. After more intensive therapy was instituted, 50 per cent of those dying were over ten years of age. Early recognition of the disease with subsequent intensive therapy will thus significantly improve the outlook for many children. If the disease is severe and the infection overwhelming, however, some will die in infancy. Those recovering from meconium ileus have the same prognosis.

*Mucomyst manufactured by Mead Johnson Company, Evansville, Indiana.

†MistO_2Gen, Incorporated, 2711 Adeline Street, Oakland, California.

Cystic Fibrosis Center, Childrens Hospital, 4614 Sunset Boulevard, Los Angeles, California 90027.

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